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PSYCHOBIOLOGICAL MODEL OF PERSONALITY AND PSYCHOPHARMACOTHERAPY OUTCOMES IN TREATMENT OF DEPRESSION AND SCHIZOPHRENIA

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SUMMARY

In distinguishing why some patients respond and other do not respond to treatments arraised the clinically very important body of research considering weather patients' personality characteristics might predict outcomes of pharmacotherapeutic treatment. Personality can be a predictor of a psychiatric disorder either owing to their common genetic background or because it enhances exposure of the subject to environmental risk factors.

The results of the studies using psychobiological model are reviewed. The studies show that personality temperament dimension Harm Avoidance and character dimension Self-directedness predict outcomes of the pharmacological treatment of depression, but the result for other psychiatric disorders are sparse.

The studies are not straightforward in recommendations for treatment choice dependent of personality dimensions.

Key words: *personality - psychobiological model – depression – schizophrenia – adherence - treatment-resistance*

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INTRODUCTION

Despite the significant advancement in the development of psychopharmacotherapy there is still a significant proportion of patients that cannot reach or sustain remission (Mulder 2002).

Attempts to distinguish why some patients respond and others do not respond to treatments has led to the clinically very important research weather and which patients' characteristics lead to favorable vs. unfavorable treatment outcomes. The idea that personality may influence the outcome of psychiatric disorders is not new. Even Kraepelin and Freud speculated that personality pathology might be related to the etiology and presentation of depression, but also to its responsiveness to treatment interventions (Ilardi & Craighead 1995, Mulder 2002).

Personality comprises those characteristics of the person that account for consistent patterns of feeling, thinking and behavior (Pervin & John 1996). Several models have been proposed for classifying personality. One of the most commonly used is Cloninger's psychobiological model (Cloninger et al. 1993). It includes temperament and character dimensions to measure personality and specifies 4 homogeneous dimensions of temperament: Harm Avoidance (HA), which is defined as pessimistic worrying in anticipation of problems; Novelty Seeking (NS), which describes the initiation of the appetitive approach in response to novelty; Reward Dependence (RD) which describes the maintenance of the behaviour in response to cues of social reward and Persistence (P), which is defined as perseverance despite frustration and fatigue. The three character dimension in the model are: Self-Directedness (SD) defined as having will-power and determination, Cooperativeness (C) that describes individual differences with regard to tolerance and empathy and Self-Transcendence (ST) that characterizes individual differences in spirituality (Cloninger et al. 1994). This model rose actually from the attempt to integrate the ideas about neurotransmitter systems into comprehensive personality model (Cloninger 1987). Accordingly, the temperament dimensions have been associated with activity of particular neurotransmitter systems: Harm Avoidance with serotonin, Novelty Seeking with dopamine and Reward Dependence with norepinephrine. Besides, temperament fulfils all criteria for an endophenotype; it is moderately heritable (Heath et al. 1994, Stallings et al. 1996), exhibits parallels between affected and non-affected family members compared with the general population (Savich et al. 2008, Jacobs et al. 2009), and has an association with major psychiatric disorders in the general population (Cloninger et al. 1994, Cloninger et al. 2006). In psychiatry research, the endophenotype approach is suggested to be a shift from the categorical conceptualizations of diagnostic categories to a more homogeneous presentation of the underlying vulnerability (Berretini 2005). Accordingly, temperament may relate to treatment adherence and social and clinical outcome of the illness.

Personality may affect overall treatment response or response to certain treatment modalities or influence which treatments patients receive. In this article we shall discuss studies that assessed associations between the factors that affect treatment response as adherence and placebo response and two major categories of psychiatric disorders, depression and schizophrenia, with personality dimensions and treatment outcomes.

ADHERENCE AND PERSONALITY

Studies report non-adherence rates ranging from 20% to 89%, and mention it as the most important determinant of relapse in patients with schizophrenia

(Gilmer et al. 2004) as well as in depression (Beland et al. 2011). Adherence behavior is influenced by patient, environment, and treatment factors. Patient factors such as ethnicity, age, cognitive functioning, degree of insight, symptom constellation, and substance abuse have been reported to influence adherence (Weiden 2007). Our results showed that the Novelty Seeking temperament dimension, associated with impulsivity, curiosity, attention seeking and self-indulgence, was correlated with medication non-adherence (Aukst Margetic et al. 2010). Similar results as ours were shown in the article of Liraud and Vardaux (2001), which used Sensation Seeking (Zuckerman et al. 1978) as a measure of temperament and found that patients with psychosis and major depression with higher Sensation Seeking have an increased risk of poor medication adherence. The subscale of Novelty Seeking, Exploratory excitability vs. Stoic rigidity consists of items that assess a dislike of repetition, intolerance of routine and a restless reaction to monotony. They are easily bored, and subjects presenting these temperamental characteristics may be more reluctant to accept the need of taking medication on a regular basis. The sedative effect of psychotropic drugs, which appears immediately, is hardly tolerant by novelty seekers as well. An interesting finding is that the character dimension of Cooperativeness was not associated with adherence levels (Aukst Margetić et al. 2010). In clinical practice, exploring these temperamental characteristics may be helpful to better identify patients at high risk for poor medication adherence not only in psychiatric but in various chronic diseases (Aukst Margetić et al. 2010). Internalized stigma, a concept associated with poor outcomes of schizophrenia, among others to poor adherence, was also predicted by personality dimensions e.g. Harm Avoidance and Self-directedness (Aukst Margetić et al. 2010). A similar concept, therapeutic alliance, in early patients with schizophrenia has been associated with Big Five dimension Agreeableness (Johansen et al. 2013).

PLACEBO RESPONSE AND PERSONALITY

Growing placebo response has been increasing to one of a leading problems of current clinical studies. Because of the large variation in the size of the placebo response (Watson et al. 2012), it seems likely that some personality traits might have a moderating role in placebo responding (Jakšić et al. 2013). Additionally, individuals with mostly negative attitudes ('pharmacophobics') and those with mostly positive attitudes ('pharmacophilics') towards pharmacotherapy exhibit differences with regard to some personality traits (Jakšić et al. 2013, Emilsson et al. 2011). There are evidence of overlapping underlying biological processes between personality traits and size of placebo response. Endogeous opioid system and dopaminergic system play crucial role in neurobiology of placebo analgesia (Oken 2008). Dopamine, which is proposed as the leading neurotransmitter regulating the reward system, is released in the ventral striatum during the actual experience of placebo analgesia, and also during the anticipation of placebo-induced pain relief (Scott et al. 2007). Schweinhardt et al. (2009) showed that dopamine-related traits as Novelty Seeking accounted for 30% of the variance in the placebo analgesic response. Negative expectations, on a contrary, show association with nocebo effect. Neuroticism, a trait similar to Harm avoidance and a predictor of anxiety, pessimism and worry, was a negative predictor of placebo responding (John & Srivastava 1999). Harm avoidance was also associated with pain sensitivity in various population of acute, chronic and malignant diseases (Conrad et al. 2007, Aukst Margetić et al. 2013)

DEPRESSION

In the treatment of major depression, the acute response to antidepressants or cognitive behavioral therapy is only moderate. Substantial improvement occurs in about 50% to 65% of patients receiving active treatment, compared to 30% to 45% in placebo-control subjects. Most patients with major depression, who do improve, acutely have recurrences within the next three years, despite the use of medications and/or cognitive-behavioral therapy (Walsh et al. 2002). In subjects who drop out or prematurely discontinue treatment (which is a frequent case), the relapse is more rapid. Some the factors influencing those issues are nevertheless personality constructs and presence of personality disorder. However, discussing the associations between personality and outcome we can distinguish clinically relevant outcomes in treating patients with depression with a particular drug, and how they respond to drug treatment in general.

Results considering associations between personality dimensions and treatment with particular single drug consider mostly results with temperamental dimensions. A great deal of studies used the Tridimensional Personality Questionnaire (TPQ), the instrument that preceded TCI. Joffe et al. (1993) reported that high Harm Avoidance scores predicted worse outcome in depressed outpatients, and Mulder et al. (2009) that high Harm Avoidance was associated with higher rates of relapse. The study by Joyce et al. (1994) found that temperament accounted for 35% of the variance in outcome in depressed outpatients.

In addition, women with high Harm Avoidance scores responded preferentially to desipramine, while those with high Reward Dependence scores responded preferentially to clomipramine. These results suggested that personality might prove clinically useful in helping to decide which drug to give to which patient. In a small study that partly replicated these results, Nelson and Cloninger (1995) initially reported that Reward Dependence accounted for 37% of the variance in percentage change in depressive symptoms. In a much larger study (Nelson & Cloninger 1997), those two authors reported that lower RD scores predicted better response to

nefazodone, but this result only explained 1% of the variance in outcome measures and was in the opposite direction from the Joyce et al. (1994) study. One study reported that low Harm Avoidance and high Reward Dependence scores predicted better outcome in an open paroxetine trial (Tome et al. 1997), but another found that TPQ scores were unrelated to response (Sato et al. 1999). A Newman and colleagues' attempt to replicate the Joyce et al. (1994) study failed to find any relationship between TPQ scores and depression outcome (Newman et al. 2000).

Temperament dimension Harm Avoidance scores appear to be related to depression severity (Mulder & Joyce 1994) and decrease with successful treatment in all the studies that have reported on this (Berlanga 1999, Mulder & Joyce 1994, Brown et al. 1992, Kampman & Poutanen 2011, Quilty et al. 2010). The other temperament dimensions, Novelty Seeking and Reward Dependence, appear to be relatively unaffected (Kampman & Poutanen 2011). The most of the studies used antidepressants from the class of SSRI or clomipramine targeting serotonergic system, presumed to be associated with Harm Avoidance. The obvious question therefore is whether Harm Avoidance reflects personality characteristics that may affect recovery or whether they are subclinical depression symptoms that are related to poorer recovery and a higher chance of relapse.

Several studies (Spittlehouse et al. 2010, Sato et al. 1999) have used the expanded model with seven dimensions of temperament and character to predict response; the authors reported that the character measures of Self-directedness and temperament dimension Harm Avoidance predicted better response, but it was not uniform finding. The only difference in the effect on TCI dimensions between fluoxetine, imipramine and placebo in the study of Agosti & McGrath (2002) was the decrease of Self-transcendence in the fluoxetine group. In a study of Mulder et al. (2009) those who relapsed after 6 months of follow up had higher Harm Avoidance and lower Self-directedness vs. non relapses. The authors suggested that the relationship between the relapse proneness and characterological dimension Self-directedness, may be partially explained with its reciprocal relationship with high Harm Avoidance (Mulder et al. 2009). Studies also showed that all personality changes do not start at the same time e.g. early changes occurring in the first month of treatment consider decreasing of Harm Avoidance and delayed changes consider increasing of Self-directedness and maybe decrease in Self-transcendence (Corruble et al. 2002).

High HA also indicates suseptability to depression. In the study of Farmer et al. (2003) comparison of HA scores between depressed patients and their siblings showed stable trait-like characteristics that were likely related to the genetic susceptibility to depression.

Genetic studies showed the association between Harm avoidance and 5-HTTLPR polymorphism (short allele) as well as amygdala hyperreactivity (Ebstein 2006), that have been previously related with response to antidepressant treatment (Huezo-Diaz et al. 2009).

Accordingly, results support four types of potent relationships between Harm Avoidance and depression: an influence of state (depression) on trait measure (HA), a pathoplastic effect of Harm Avoidance on depressive expression, a vulnerability model (Harm Avoidance representing a susceptibility factor for depression), and a scar model with elevated Harm Avoidance scores even after remission of acute depressive symptoms.

SCHIZOPHRENIA

Studies that assess the associations between personality, treatment outcomes and schizophrenia are fewer in number (Miettunen & Raevuori 2011). One of them is study of Strakowsky (1995) that considered the relationship of Tridimensional Personality Questionnaire measures with outcome. They reported higher Harm Avoidance as the measure of postpsychotic depression and that high Novelty Seeking scores in manic patients at discharge predicted poorer functional recovery (Strakowsky et al. 1993, Strakowsky et al. 1995). There were no studies so far that assessed effect of treatment to personality dimension in this group of patients. Personality trait Harm Avoidance may be associated with a vulnerability to schizophrenia and heterogeneity of the outcome in this disorder (Lysaker et al. 2004, Aukst Margetic et al. 2010). PET studies have found associations between D2/D3 receptor availability in brain regions such as striatum, insula and amygdala, and anxiety-related personality measures, most often Harm Avoidance (Yasuno et al. 2001, Harro 2010).

Although dimension Novelty Seeking has been associated with dopamine activity in early studies (e.g dopamine receptor D4) (Ebstein et al. 1996, Benjamin et al. 1996), several studies failed to replicate the associations between novelty seeking and dopaminergic transmission (Ebstein 2006). This issue remains controversial (Munafo et al. 2008) implicating that self-report measures do not quite catch the biological constructs, considering extreme complexity of the psychiatric disorders' phenotypes.

Although the results are promising, there are inconsistencies in the findings. Some authors mention the limitation of the usage of all self-report measures of personality as they are based on assumption that you just have to ask if you want to know somebody's characteristics (Mulder 2002). Accordingly, data especially from molecular genetics of personality show larger variability implicating that self-report measures do not completely catch the underlying biological processes and should be further improved and combined with other markers of endophenotype (Ebstein 2006).

CONCLUSION

The knowledge about patient's personality offers significant insight in patients' structure behavior and

various treatment outcomes. The studies are consistent that in fighting depression, a treatment that could lower Harm Avoidance would be invaluable (Mulder et al. 2009).

But, studies are definitively not straight in recommendations for treatment choice, especially psychopharmacological, in patients with depression or even less in schizophrenia.

More research in personality dimensions' concepttualizations as phenotype characteristics has to be made to lead to better utility in everyday's clinical work.

Clinical psychopharmacology would greatly benefit from an ability to predict individual sensitivity to a particular medicine. More insight in interindividual diferences based on personality traits or their neurobiological correlates may lead to new drug developement exspecialy in the area of therapeutic resistance or drugs active in subset of depressive patietns.

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